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(54) **PROCESS FOR THE PREPARATION OF ROSUVASTATIN**

VERFAHREN ZUR HERSTELLUNG VON ROSUVASTATIN

PROCEDE DE PREPARATION DE ROSUVASTATINE

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(56) References cited:
EP-A- 0 521 471

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Description

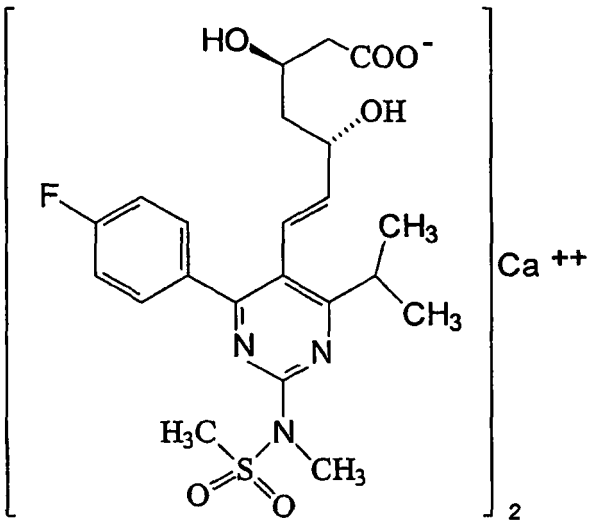
FIELD OF THE INVENTION

[0001] The present invention relates to a process for the preparation rosuvastatin, a promising new HMG-CoA reductase inhibitor.

BACKGROUND OF THE INVENTION

[0002] HMG-CoA reductase inhibitors, popularly known as statins, are among the most widely prescribed lipid - lowering drugs.

[0003] Chemically rosuvastatin is (+)-(3R,5*S*)-7-[4-(4-Fluorophenyl)-6-isopropyl-2-(N-methyl-N-methanesulfonylamino)pyrimidin-5-yl]3,5-dihydroxy-6(E)-heptenoic acid calcium salt (2:1) having the structural formula I.



FORMULA I

[0004] Rosuvastatin is an antihypercholesterolemic drug used in the treatment of atherosclerosis.

[0005] Hypercholesterolemia is now well recognized as a primary risk in coronary heart disease. Clinical studies with lipid lowering agents have established that decreasing elevated serum cholesterol level reduces the incidence of cardiovascular mortality. Recently, it has been found that rosuvastatin calcium has consistently shown greater potency than other currently marketed statins (atorvastatin, simvastatin and pravastatin) in preclinical and clinical testing.

[0006] Rosuvastatin and a process for its preparation is disclosed in U.S. Patent No. 5,260,440. The process disclosed therein involves four distinct chemical steps: (1) condensation of methyl (3R)-3-[(*tert*-butyldimethylsilyl) oxy]-5-oxo-6-triphenylphosphoranyli- dene hexanoate with 4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methanesulfonylamino)-5-pyrimidinecarboxaldehyde; (2) deprotection of the 3-hydroxyl group to give the keto alcohol; (3) reduction of 5-oxo to get the chiral dihydroxy heptenoate; and (4) hydrolysis of the dihydroxy heptenoate.

[0007] The generation of the phosphorane side chain requires eight synthetic steps and involves expensive reagents. The process is both uneconomical and time consuming, hence not suitable for commercial production.

[0008] It is, therefore, desirable to provide an efficient process for the preparation of rosuvastatin which improves the economics by employing less expensive reagents and is more productive.

SUMMARY OF THE INVENTION

[0009] The present invention provides a process and novel intermediates for the preparation of rosuvastatin, its salts, esters, or the corresponding cyclized lactone form. The process provides obvious benefits with respect to economics and convenience to operate on a commercial scale.

DETAILED DESCRIPTION OF THE INVENTION

[0010] The present invention provides a process for the preparation of rosuvastatin of structural formula I as shown in Scheme I or the corresponding ring closed lactone form, comprising:

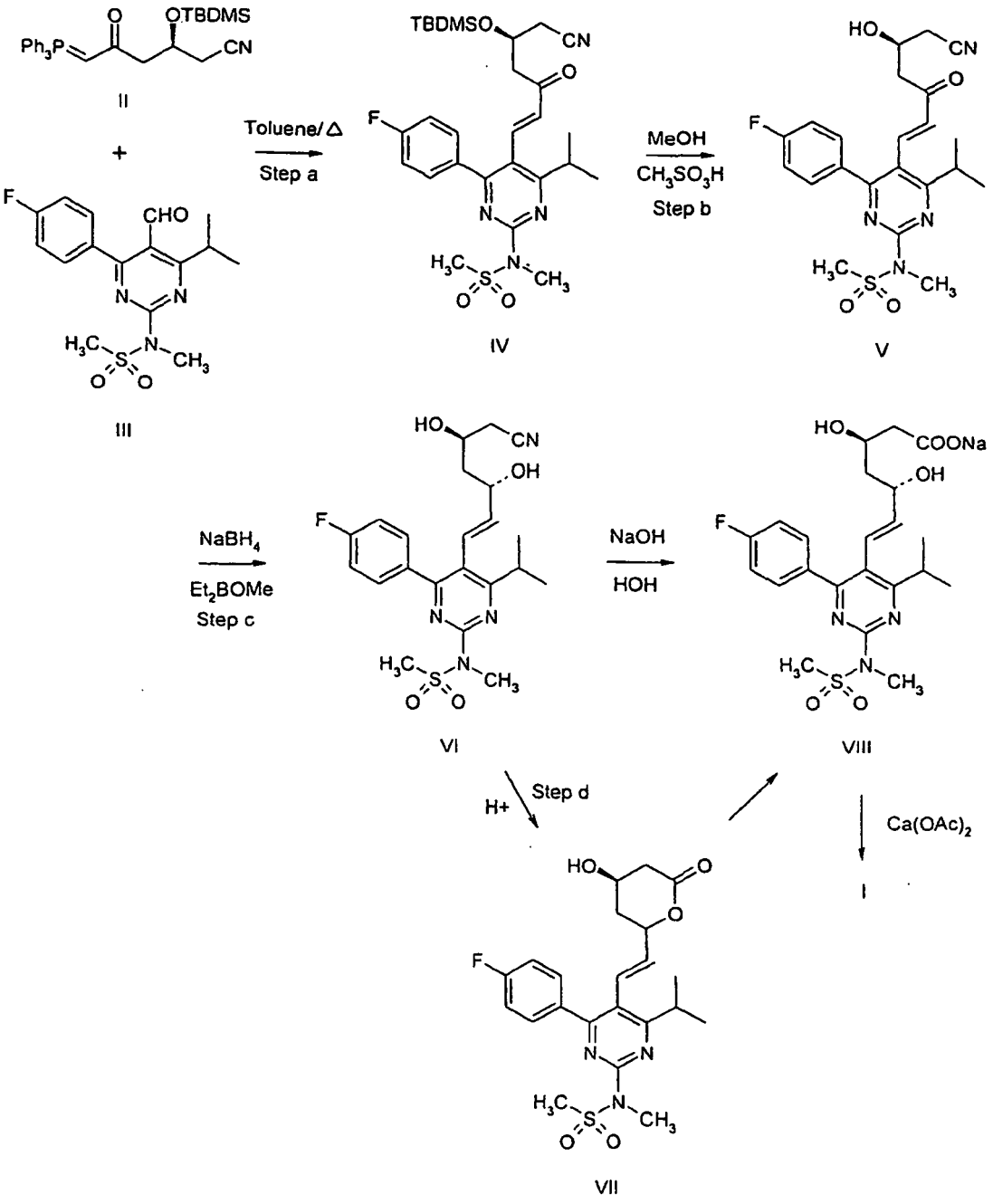
(a) condensing 1-cyano(2S)-2-[(*tert*-butyldimethylsilyl)oxy]-4-oxo-5-triphenylphosphoranylidene pentane of structural formula II with 4-(4-Fluorophenyl)-6-isopropyl-2-(N-rnethyl-N-methanesulfonylamino)-5-pyrimidinecarbaldehyde of structural formula III to give a condensed product of structural formula IV,

(b) deprotecting the tert-butyldimethylsilyl group of the condensed product to afford a cyanoketo alcohol of structural formula V,

(c) reducing the cyanoketo alcohol to cyanodiol of structural formula VI, and

(d) hydrolyzing the cyanodiol of structural formula VI to produce said compound of structural formula I in free acid form, or in the form of an ester or a lactone thereof, or in salt form.

Scheme I



[0011] The condensation at step (a) is performed in the presence of an organic solvent, especially such as toluene, benzene, cyclohexane, heptanes, acetonitrile, tetrahydrofuran, dioxane and ethyl acetate. The reaction is carried out for about 1 to about 100 hours.

[0012] The deprotection of the tert-butyldimethylsilyl group at step (b) is performed in an organic solvent in the presence of acids or tetrabutylammonium fluoride to give a cyanoketo alcohol of formula V.

[0013] The organic solvent is selected from solvents such as sulfolane, dioxane, dimethylsulfoxide, dimethylacetamide, N-methyl pyrrolidone, acetonitrile, diethyl ether, tetraydrofuran,dimethylformamide, and lower alcohols such as methanol, ethanol, propanol.

[0014] The acids used for deprotection are selected from sulfonic acids such as methanesulfonic acid, trifluoromethane

sulfonic acid, inorganic acids such as hydrochloric acid, sulfuric acid nitric acid, phosphoric acid and organic acids such as formic acid, trifluro acetic acid, acetic acid.

[0015] The cyanoketo alcohol of formula V obtained in step (b) is reduced with diethylmethoxyborane and sodium borohydride. The reduction is performed in an organic solvent mixture comprising alcohols and non-alcoholic sovents. The reaction is worked up after completion to afford cyanodiol of formula VI.

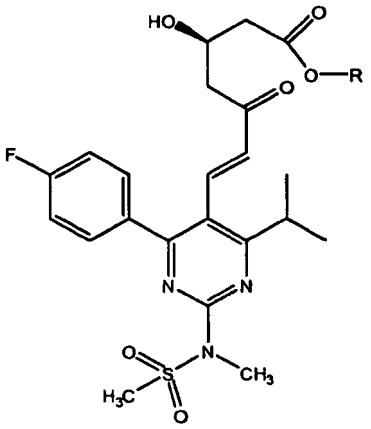
[0016] The organic solvent mixture includes alcohols such as methanol, ethanol, propanol and butanol. The non-alcoholic organic solvent includes solvents such as acetonitrile, diethyl ether, tetrahydrofuran and dimethylformamide.

[0017] The reaction at step (c) is performed at a temperature from about -100°C to about 20°C, for example from about -80°C to about -70°C under cooling for about 10 minutes to about 20 hours, for example for about 30 minutes to about 10 hours.

[0018] The cyanodiol of formula VI is hydrolyzed by acids at step (d) to afford lactone of formula VII. Acids, which may be used, include inorganic acids such as hydrochloric acid, sulfuric acid and the like. The cyanodiol of Formula VI can be directly converted to its sodium salt of formula VIII.

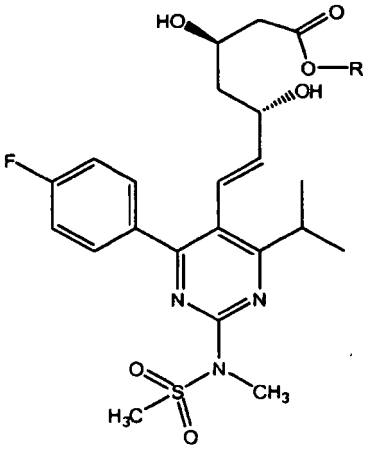
[0019] The lactone obtained in step (d) is converted into its sodium salt of formula VIII and then to its hemicalcium salt of rosuvastatin of formula I by treatment with calcium acetate.

[0020] In another aspect of the invention, rosuvastatin is prepared by a process which comprises treatment of the condensed product of structural formula IV with an alcohol, such as methanol, ethanol, propanol, and an acid such as hydrochloric acid to provide an ester of formula IX



Formula IX

wherein R is methyl, ethyl or propyl;
which is reduced to provide a compound of formula X,



Formula X

wherein R is methyl, ethyl or propyl
which in tum, is hydrolyzed to give rosuvastatin by the same method as described in steps (c) and (d) of Scheme I.

[0021] The starting material of formula III may be prepared, for example, as described in U.S. Patent No. 5,260,440.

[0022] The methods known in the art may be used with the process of this invention to enhance any aspect of the process. The product obtained may be further purified
by any technique known to a person skilled in the art, for example, crystallization, column chromatography, preparative high pressure liquid chromatography, preparative thin layer chromatography, extractive washing in solution or a combination of these procedures.

[0023] In the following examples, the preferred embodiments of the present invention are described only by way of illustrating the process of the invention. However, these are not intended to limit the scope of the present invention in any way.

EXAMPLES

[0024] Preparation of rosuvastatin (+)-(3R, 5S)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methanesulfonylamino)pyrimidin-5-yl]-3,5-dihydroxy-6(E)-heptenoic acid calcium salt (2:1).

EXAMPLE 1

Step A

Preparation of condensed product N-[5-[-(tert-Butyl-dimethyl-silanyloxy)-6-cyano-3-oxo-hex-1-enyl]-4-(4-fluorophenyl)-6-isopropyl-pyrimidin-2-yl]-N-methyl-methanesulfonamide (Condensed product, Formula IV)

[0025] To a solution of pyrimidine aldehyde (1.0gm) of Formula III in toluene (20ml), 1-cyano (2S)-2-[(tert-butyldimethylsilyl)oxy]-4-oxo-5-triphenylphosphoranylidene pentane of formula II was added and the reaction mixture was refluxed for about 24 hours. The reaction mixture was concentrated and the residue titurated with cyclohexane (50ml). The cyclohexane layer was concentrated to give a residue which was purified by silica gel chromatography, eluted with toluene to obtain 1.60gm of the condensed product as a thick oil.

Step B

Preparation of cyanoketo alcohol-N-[5-(6-cyano-5-hydroxy-3-oxo-hex-1-enyl)-4-(4-fluoro-phenyl)-6-isopropyl-pyrimidin-2-yl]-N-methyl-methanesulfonamide (Cyanoketo alcohol, Formula V)

[0026] To a solution of the condensed product (1.0gm) in methanol (10ml), a solution of (0.8ml) of methanesulfonic acid in water (4.6% w/w) was added dropwise at 10-15°C. The reaction mixture was stirred for 24 hours at room temperature, concentrated and the residue was dissolved in methylene chloride (10ml). The solution was washed with 1% sodium bicarbonate followed by brine. The organic layer was concentrated to give a residue which was purified by column chromatography over silica gel, eluted with toluene to give (0.65gm) cyanoketo alcohol as a solid.

Step C

Preparation of cyanodiol N-[5-(6-cyano-3,5-dihydroxy-hex-1-enyl)-4-(4-fluoro-phenyl)-6-isopropyl-pyrimidin-2-yl]-N-methyl-methanesulfonamide. (Cyanodiol, Formula VI)

[0027] To a solution of the cyanoketo alcohol (1.0 g) in tetrahydrofuran (THF) (25ml), methanol (7ml) was added and the solution was cooled to -78°C. Diethylmethoxy borane (2.3ml) in THF (1 M) at -76°C to -78°C was added to the reaction mixture. The reaction mixture was stirred for 30 min and sodium borohydride (0.10gm) was added. The reaction mixture was further stirred at the same temperature for 3 hours and the temperature was allowed to rise to 25°C in 45 minutes. Acetic acid (1.4m1) was added and stirred for 10 min. The solvent was evaporated under vacuum and then methanol (10ml) was added which was also evaporated off. Ethyl acetate (10ml) was added and the solution was washed with aqueous sodium bicarbonate solution (3ml). The organic layer was washed with brine (5ml) and then dried over sodium sulfate. The concentration of the solution under reduced pressure yielded cyanodiol as oil (0.8 gm).

Step D

Reparation of Rosuvastatin

[0028] Conc. HCl (2.5ml) was added to the cyanodiol (0.5gm) and the reaction mixture was stirred at room temperature for 12 hours. The resulting solution was diluted with water (2.5ml), cooled to 5°C and then neutralized with 1% aqueous sodium bicarbonate. The resulting mixture was extracted with ethyl acetate (10ml). The ethyl acetate layer was concentrated and the resulting residue was dissolved in toluene (10ml). The toluene solution was refluxed for 2 hours and the solvent was evaporated to give rosuvastatin lactone. Ethanol (7ml) was added to the residue and stirred for 60 min followed by the addition of 0.1N aqueous NaOH(11ml). Ethanol was evaporated under vacuum, followed by the dropwise addition of a solution of calcium acetate. After stirring for 2 hours, the product was filtered, washed and dried to give rosuvastatin hemicalcium salt (0.26 g).

EXAMPLE 2

Preparation of rosuvastatin from methyl ester of Formula IX

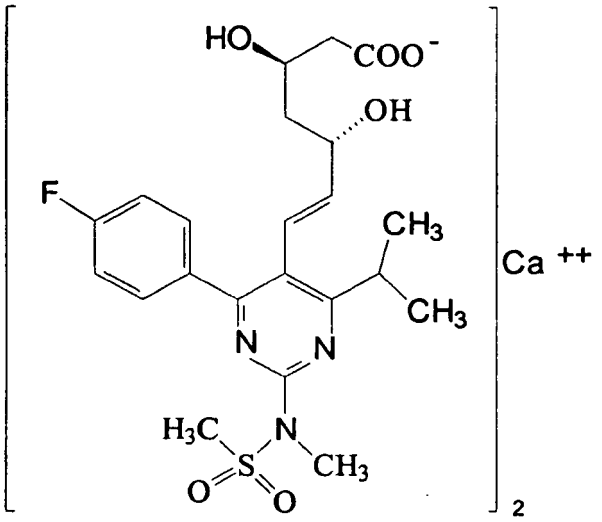
[0029] HCl gas was bubbled into a suspension of the condensed product (1.0 gm) of formula IV in methanol (10ml) at -40°C to -20°C for 2.5 hours. The resulting solution was stirred at 0°C for 15 hours and then the solvent was removed. The residue was taken in ethyl acetate and washed with water (10ml). The pH of the organic layer was adjusted to 4.5 with aqueous sodium bicarbonate. The ethyl acetate layer was separated, washed with water and then with brine. The organic layer was concentrated to give a residue which was purified by column chromatography over silica gel to give 0.8gm methyl ester of formula IX.

[0030] The methyl ester obtained above was reduced in the same way as described in step (c) of Example 1. Subsequent hydrolysis to the acid, its sodium salt formation and further conversion to the calcium salt was prepared as described in step (d) of Example 1 which afforded rosuvastatin hemicalcium salt (0.5g).

[0031] While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

Claims

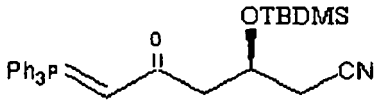
1. A process for producing rosuvastatin of structural formula I,



FORMULA I

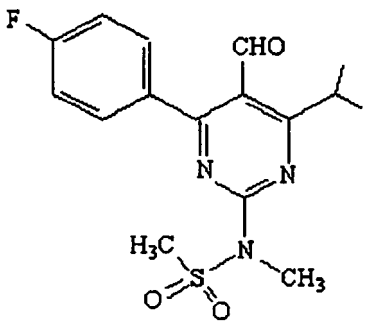
comprising:

a. condensing 1-cyano (2S)-2-[(tert-butyldimethylsilyl)oxy]-4-oxo-5-triphenylphosphoranylidene pentane of structural formula II



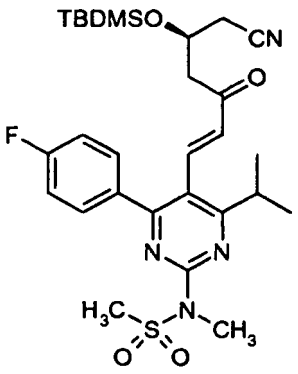
FORMULA II

with 4-(4-Fluorophenyl)-6-isopropyl-2-(N-methyl-N-methanesulfonylamino)-5-pyrimidinecarbaldehyde of structural formula III



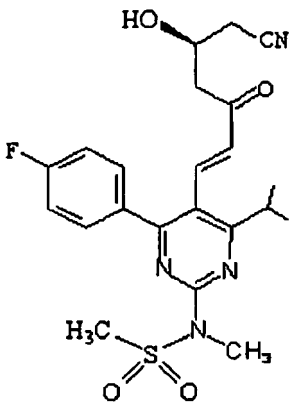
FORMULA III

to give a condensed product of structural Formula IV,



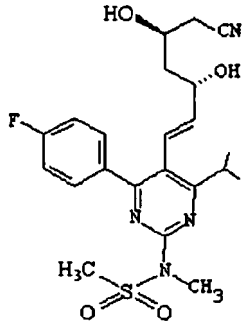
FORMULA IV

b. deprotecting the tert-butyldimethylsilyl group of the condensed product to afford a cyanoketo alcohol of structural formula V,



FORMULA V

c. reducing the cyanoketo alcohol to cyanodiol of structural formula VI, and



FORMULA VI

d. hydrolyzing the cyanodiol of structural formula VI to produce said compound of structural formula I in free acid form, or in the form of an ester or lactone thereof, or in salt form.

2. The process of claim 1 wherein step (a) is carried out in an organic solvent.

3. The process of claim 2 wherein the organic solvent is selected form the group consisting of toluene, benzene, cyclohexanes,heptanes or mixture(s) thereof.

4. The process of claim 3 wherein the organic solvent is toluene.

5. The process of claim 1 wherein step (b) is performed in an organic solvent.

6. The process of claim 5 wherein the organic solvent is selected from the group consisting of sulfolane, dioxane, dimethyl sulfoxide, dimethyl acetamide, N-methyl pyrrolidone, acetonitrile, diethyl ether, tetrahydrofuran; dimethyl-formamide, methanol, ethanol, propanol, and mixtures thereof.

7. The process of the claim 6 wherein the organic solvent is methanol.

8. The process of clam 1 wherein the deprotection at step (b) is performed by treating with acids or tetrabutylammonium fluoride.

9. The process of claim 8 wherein the acids are sulfonic acids, inorganic or organic acids.

10. The process of claim 9 wherein the acids are selected from the group consisting of methanesulfonic acid, trifluor-omethanesulfonic acid, hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid, formic acid, trifluroacetic acid, and acetic acid.

11. The process of claim 10 wherein the acid is methanesulfonic acid.

12. The process of claim 1 wherein the reduction at step c is carried out in the presence of diethylmethoxyborane and sodium borohydride.

13. The process of claim 12 wherein the reduction is performed in an organic solvent mixture comprising alcohol and non-alcoholic solvents.

14. The process of claim 13 wherein the alcohol is selected from the group consisting of methanol, ethanol, propanol and butanol.

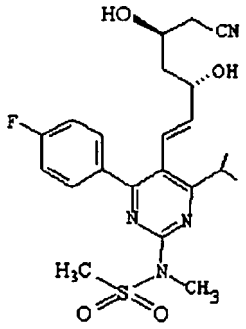
15. The process of claim 14 wherein the alcohol is methanol.

16. The process of claim 13 wherein the non-alcoholic organic solvent is selected from the group consisting of acetonitrile, diethyl ether, tetrahydrofuran and dimethylformamide.

17. The process of claim 16 wherein the non-alcoholic organic solvent is tetrahydrofuran.

18. The process of claim 1 wherein the hydrolysis at step (d) is performed after the reaction at step c is completed.

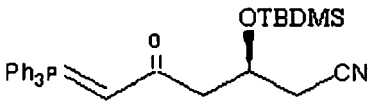
19. A process for preparing a compound of structural formula VI



FORMULA VI

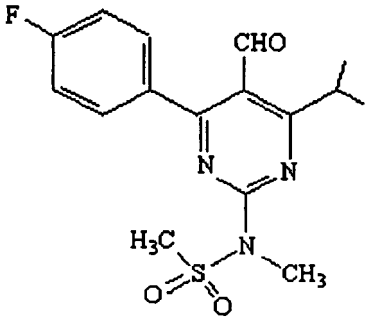
comprising:

a. condensing 1-cyano (2S)-2-[(tert-butyldimethylsilyl)oxy]-4-oxo-5-triphenylphosphoranylidene pentane of structural formula II



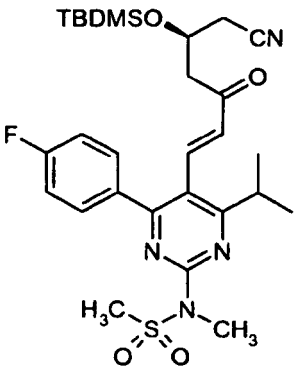
FORMULA II

with 4-(4-Fluorophenyl)-6-isopropyl-2-(N-methyl-N-methanesulfonylamino)-5-pyrimidinecarbaldehyde of structural formula III



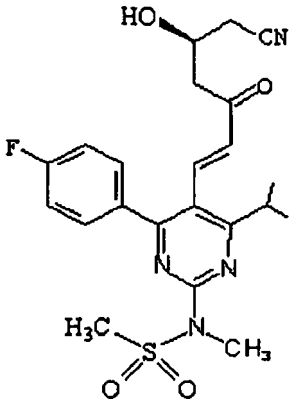
FORMULA III

to give a condensed product of structural formula IV,



FORMULA IV

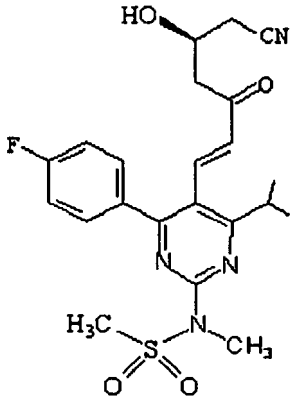
b. deprotecting the tert-butyldimethylsilyl group of the condensed product to afford a cyanoketo alcohol of structural formula V, and



FORMULA V

(c) reducing the cyanoketo alcohol of structural formula V to produce said compound of structural formula VI.

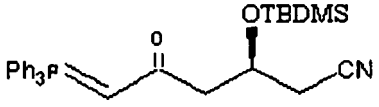
20. A process for preparing a compound of structural formula V



FORMULA V

comprising:

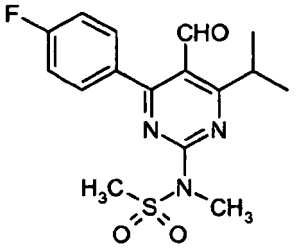
(a) condensing 1-cyano (2S)-2-[(tert-butyldimethylsilyl)oxy]-4-oxo-5-triphenylphosphoranylidene pentane of structural formula II



FORMULA II

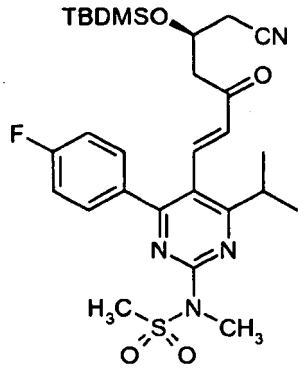
with 4-(4-Fluorophenyl)-6-isopropyl-2-(N-methyl-N-methanesulfonylamino)-5-pyrimidinecarbaldehyde of struc-

tural formula III



FORMULA III

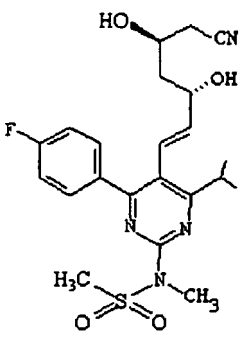
to give a condensed product of structural formula IV, and



FORMULA IV

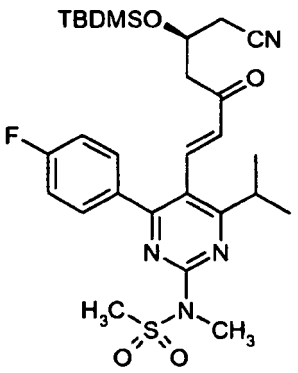
(b) deprotecting the tert-butyldimethylsilyl group of the condensed product to produce said compound of structural formula V.

21. The process of claim 20 further comprising reducing the compound of structural formula V to produce a compound of structural formula VI.



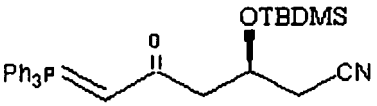
FORMULA VI

22. A process for preparing a compound of structural formula IV



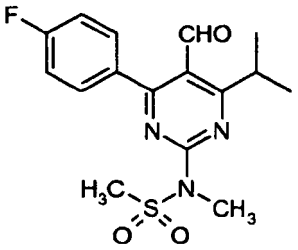
FORMULA IV

comprising: condensing 1-cyano (2S)-2-[(tert-butyldimethylsilyl)oxy]-4-oxo-5-triphenylphosphoranylidene pentane of structural formula II



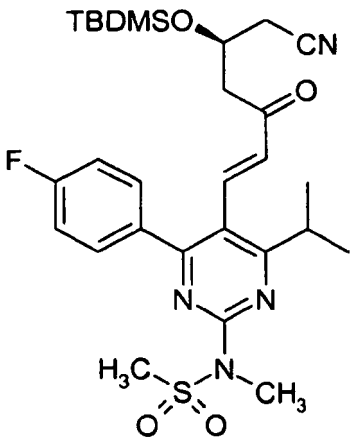
FORMULA II

with 4-(4-Fluorophenyl)-6-isopropyl-2-(N-methyl-N-methanesulfonylamino)-5-pyrimidinecarbaldehyde of structural formula III



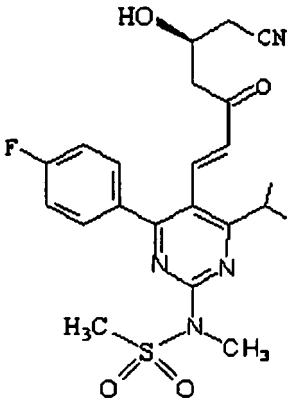
FORMULA III

to give a condensed product of structural formula IV.



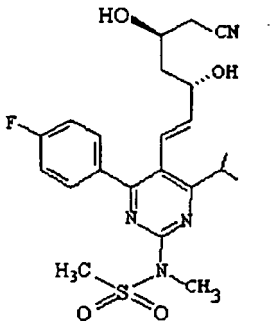
FORMULA IV

23. The process of claim 22 further comprising deprotecting the tert-butyldimethylsilyl group of the condensed product to produce a compound of structural formula V.



FORMULA V

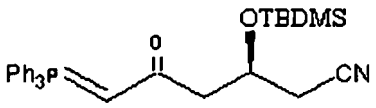
24. The process of claim 23 further comprising reducing the compound of structural formula V to produce a compound of structural formula VI.



FORMULA VI

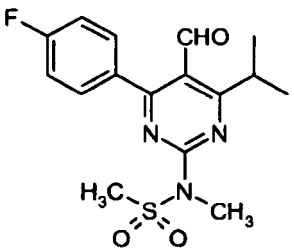
25. A process for producing rosuvastatin of structural formula I comprising:

(a) condensing 1-cyano (2S)-2-[(tert-butyldimethylsilyl)oxy]-4-oxo-5-triphenylphosphoranylidene pentane of structural formula II



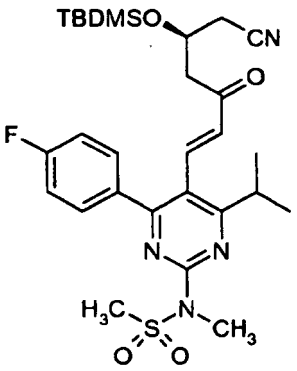
FORMULA II

with 4-(4-Fluorophenyl)-6-isopropyl-2-(N-methyl-N-methanesulfonylamino)-5-pyrimidinecarbaldehyde of structural formula III



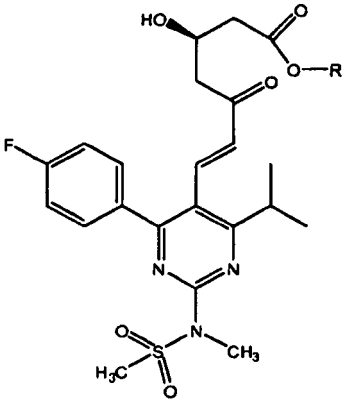
FORMULA III

to give a condensed product of structural formula IV,



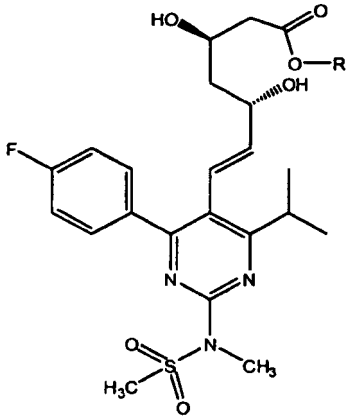
FORMULA IV

(b) esterifying the condensed product to give an ester of formula IX,



Formula IX

wherein R is methyl, ethyl or propyl;
(c) reducing the ester to compound of structural formula X, and



Formula X

wherein R is methyl, ethyl or propyl

(d) hydrolyzing the compound of structural formula X to produce said compound of structural formula I in free acid form, or in the form of an ester or a lactone thereof, or in salt form.

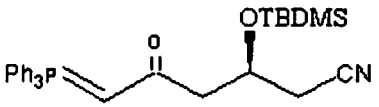
26. The process of claim 25 wherein step (a) is carried out in an organic solvent.

27. The process of claim 26 wherein the organic solvent is selected form the group consisting of toluene, benzene, cyclohexanes,heptanes or mixture(s) thereof.

28. The process of claim 27 wherein the organic solvent is toluene.

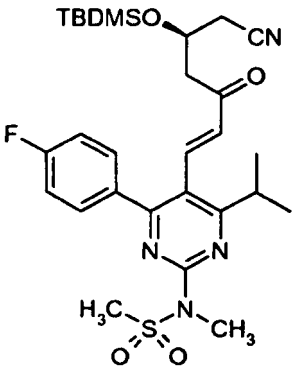
29. The process of claim 25 wherein step (b) is carried out with methanol in the presence of hydrochloric acid.

30. A compound of structural formula II.



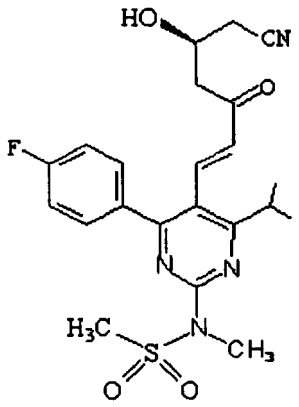
Formula II

31. A compound of structural formula IV



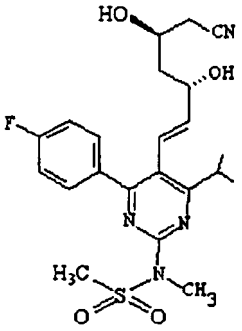
Formula IV

32. A compound of structural formula V



Formula V

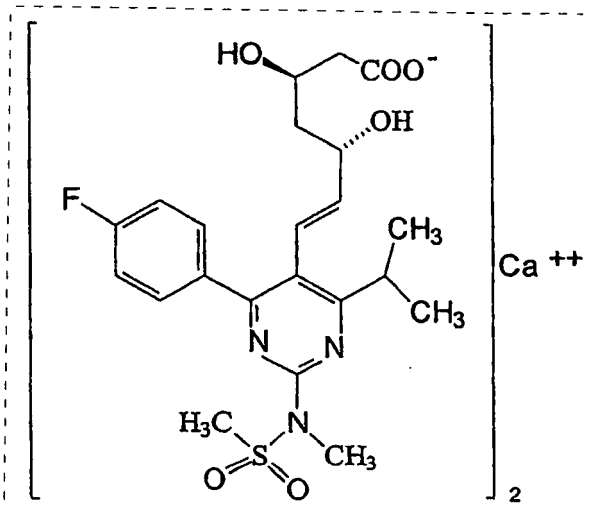
33. A compound of structural formula VI



Formula VI

Patentansprüche

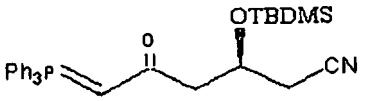
1. Verfahren zur Herstellung von Rosuvastatin der Strukturformel I,



Formel I

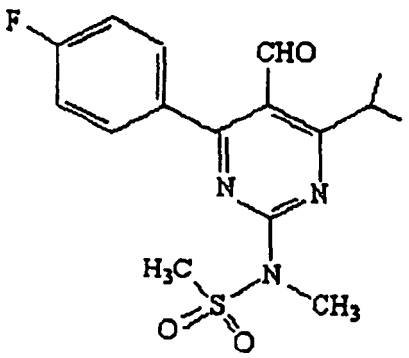
umfassend:

a: Kondensieren von 1-Cyan(2S)-2-[(t-butyldimethylsilyl)oxy]-4-oxo-5-triphenylphosphoranylidenpentan der Strukturformel II



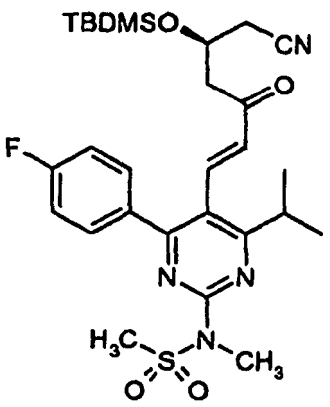
Formel II

mit 4-(4-Fluorphenyl)-6-isopropyl-2-(N-methyl-N-methansulfonylamino)-5-pyrimidincarbaldehyd der Strukturformel III



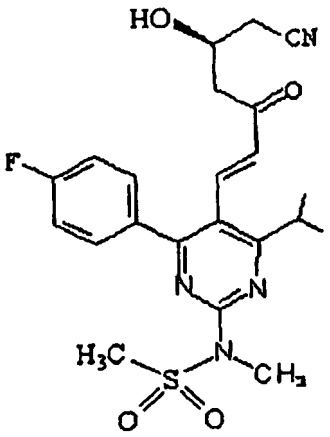
Formel III

zur Bildung eines kondensierten Produkts der Strukturformel IV,



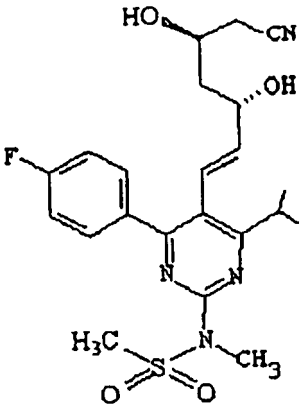
Formel IV

b: Abspalten der t-Butyldimethylsilylgruppe vom kondensierten Produkt zum Hervorbringen des Cyanketoalkohols der Strukturformel V,



Formel V

c: Reduzieren des Cyanketoalkohols zum Cyandiol der Strukturformel VI und



Formel VI

d: Hydrolyse des Cyandiols der Strukturformel VI zur Erzeugung der Verbindung der Strukturformel I in Form der freien Säure oder in Form eines Esters oder Laktons von dieser oder in Salzform.

2. Verfahren nach Anspruch 1, wobei der Schritt (a) in einem organischen Lösungsmittel durchgeführt wird.

3. Verfahren nach Anspruch 2, wobei das organische Lösungsmittel aus der aus Toluol, Benzol, Cyclohexanen, Heptanen oder deren Mischung(en) bestehenden Gruppe ausgewählt ist.

4. Verfahren nach Anspruch 3, wobei das organische Lösungsmittel Toluol ist.

5. Verfahren nach Anspruch 1, wobei der Schritt (b) in einem organischen Lösungsmittel durchgeführt wird.

6. Verfahren nach Anspruch 5, wobei das organische Lösungsmittel aus der aus Sulfolan, Dioxan, Dimethylsulfoxid, Dimethylacetamid, N-Methylpyrrolidon, Acetonitril, Diethylether, Tetrahydrofuran, Dimethylformamid, Methanol, Ethanol, Propanol oder deren Mischungen bestehenden Gruppe ausgewählt ist.

7. Verfahren nach Anspruch 6, wobei das organische Lösungsmittel Methanol ist.

8. Verfahren nach Anspruch 1, wobei die Schutzgruppenabspaltung im Schritt (b) durch Behandlung mit Säuren oder Tetrabutylammoniumfluorid durchgeführt wird.

9. Verfahren nach Anspruch 8, wobei die Säuren Sulfonsäuren, anorganische oder organische Säuren sind.

10. Verfahren nach Anspruch 9, wobei die Säuren aus der aus Methansulfonsäure, Trifluormethansulfonsäure, Salzsäure, Schwefelsäure, Salpetersäure, Phosphorsäure, Ameisensäure, Trifluoressigsäure und Essigsäure bestehenden Gruppe ausgewählt ist.

11. Verfahren nach Anspruch 10, wobei die Säure Methansulfonsäure ist.

12. Verfahren nach Anspruch 1, wobei die Reduktion im Schritt (c) in Gegenwart von Diethylmethoxyboran und Natriumborhydrid durchgeführt wird.

13. Verfahren nach Anspruch 12, wobei die Reduktion in einem organischen Lösungsmittelgemisch durchgeführt wird, das Alkohol und nicht alkoholische Lösungsmittel enthält.

14. Verfahren nach Anspruch 13, wobei der Alkohol aus der aus Methanol, Ethanol, Propanol und Butanol bestehenden Gruppe ausgewählt ist.

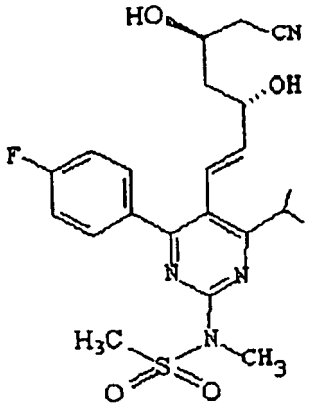
15. Verfahren nach Anspruch 14, wobei der Alkohol Methanol ist.

16. Verfahren nach Anspruch 13, wobei das nicht alkoholische organische Lösungsmittel aus der aus Acetonitril, Diethylether, Tetrahydrofuran und Dimethylformamid bestehenden Gruppe ausgewählt ist.

17. Verfahren nach Anspruch 16, wobei das nicht alkoholische organische Lösungsmittel Tetrahydrofuran ist.

18. Verfahren nach Anspruch 1, wobei die Hydrolyse im Schritt (d) durchgeführt wird, nachdem die Reaktion im Schritt (c) abgeschlossen ist.

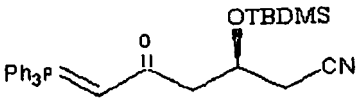
19. Verfahren zur Herstellung einer Verbindung der Strukturformel VI



Formel VI

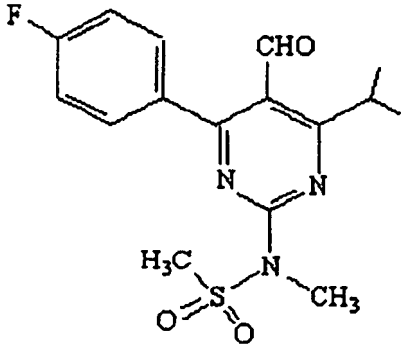
umfassend:

a: Kondensieren von 1-Cyan(2S)-2-[(t-butyldimethylsilyl)oxy]-4-oxo-5-triphenylphosphoranylidenpentan der Strukturformel II



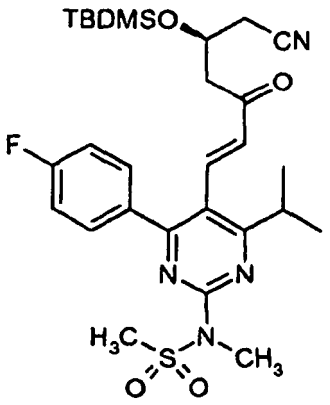
Formel II

mit 4-(4-Fluorphenyl)-6-isopropyl-2-(N-methyl-N-methansulfonylamino)-5-pyrimidincarbaldehyd der Strukturformel III



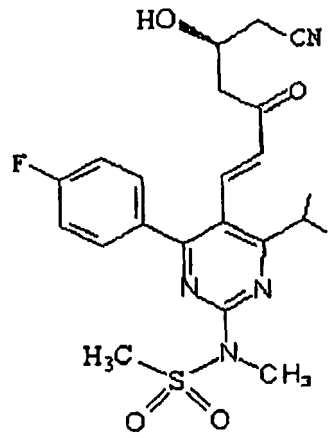
Formel III

zur Bildung eines kondensierten Produkts der Strukturformel IV,



Formel IV

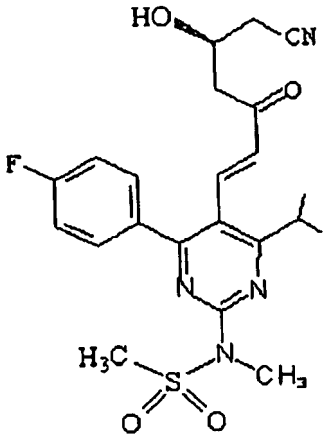
b: Abspalten der t-Butyldimethylsilylgruppe vom kondensierten Produkt zum Hervorbringen des Cyanketoalkohols der Strukturformel V,



Formel V

c: Reduzieren des Cyanketoalkohols zur Bildung der Verbindung der Strukturformel VI.

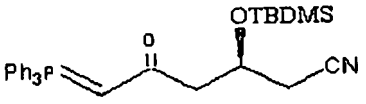
20. Verfahren zur Herstellung einer Verbindung der Strukturformel V



Formel V

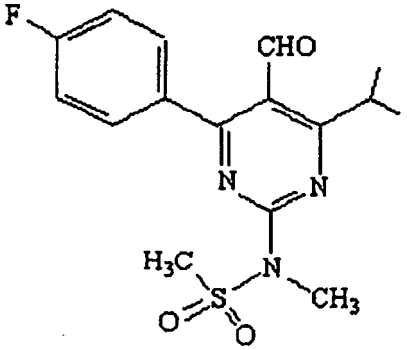
umfassend

a: Kondensieren von 1-Cyan(2S)-2-[(t-butyldimethylsilyl)oxy]-4-oxo-5-triphenylphosphoranylidenpentan der Strukturformel II



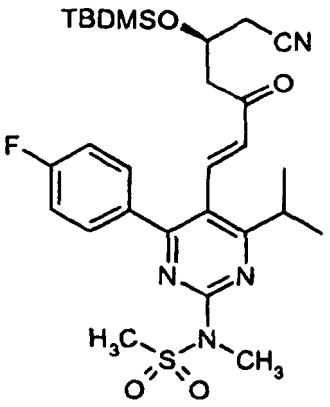
Formel II

mit 4-(4-Fluorphenyl)-6-isopropyl-2-(N-methyl-N-methansulfonylamino)-5-pyrimidincarbaldehyd der Strukturformel III



Formel III

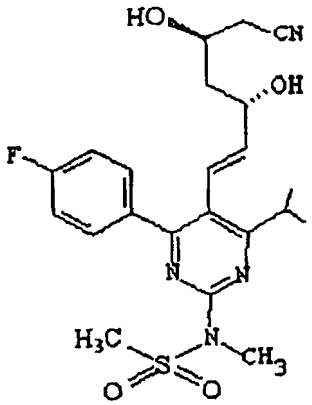
zur Bildung eines kondensierten Produkts der Strukturformel IV und



Formel IV

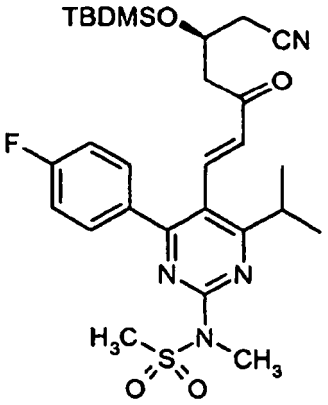
b: Abspalten der t-Butyldimethylsilylgruppe vom kondensierten Produkt zum Hervorbringen dieser Verbindung der Strukturformel V.

21. Verfahren nach Anspruch 20, ferner umfassend die Reduktion der Verbindung der Strukturformel V zur Bildung einer Verbindung der Strukturformel VI.



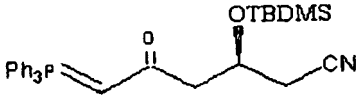
Formel VI

22. Verfahren zur Herstellung einer Verbindung der Strukturformel IV,



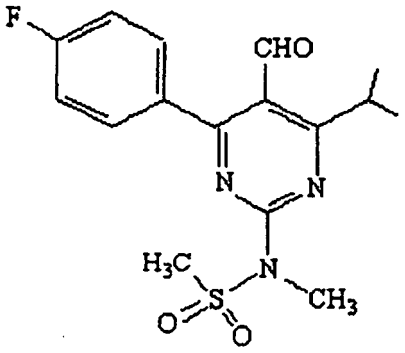
Formel IV

umfassend Kondensieren von 1-Cyan(2S)-2-[(t-butyldimethylsilyl)oxy]-4-oxo-5-triphenylphosphoranylidenpentan der Strukturformel II



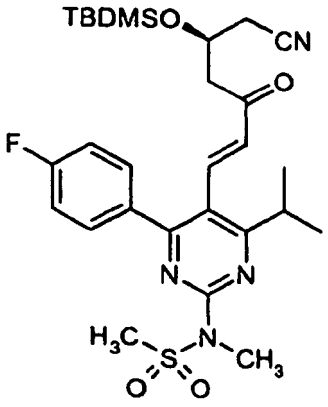
Formel II

mit 4-(4-Fluorphenyl)-6-isopropyl-2-(N-methyl-N-methansulfonylamino)-5-pyrimidincarbaldehyd der Strukturformel III



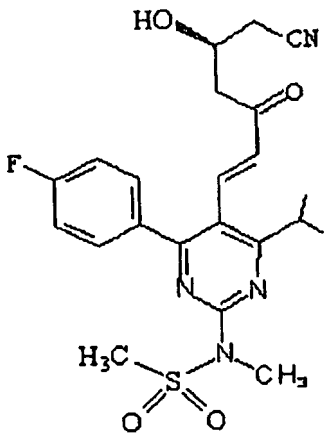
Formel III

zur Bildung eines kondensierten Produkts der Strukturformel IV,



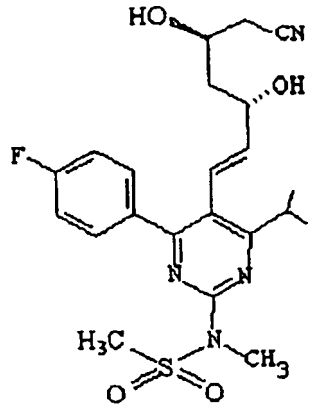
Formel IV

23. Verfahren nach Anspruch 22, ferner umfassend Abspalten der t-Butyldimethylsilylgruppe vom kondensierten Produkt zum Hervorbringen des Cyanketoalkohols der Strukturformel V.



Formel V

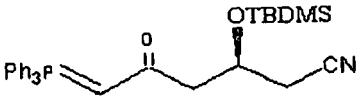
24. Verfahren nach Anspruch 23, ferner umfassend Reduzieren der Verbindung der Strukturformel V zur Herstellung einer Verbindung der Strukturformel VI und



Formel VI

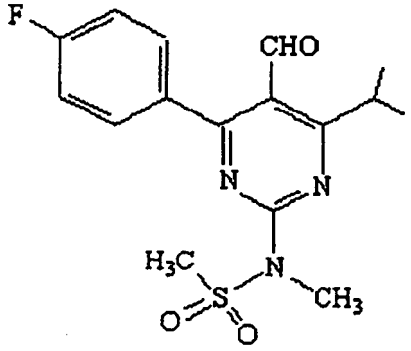
25. Verfahren zur Herstellung von Rosuvastatin der Strukturformel I, umfassend:

(a) Kondensieren von 1-Cyan(2*S*)-2-[(t-butyldimethylsilyl)oxy]-4-oxo-5-triphenylphosphoranylidenpentan der Strukturformel II



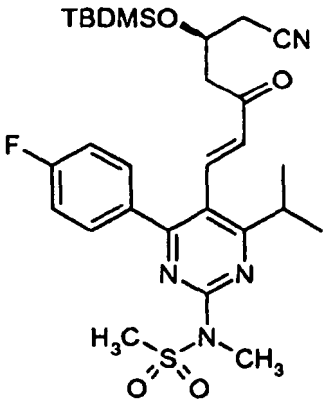
Formel II

mit 4-(4-Fluorphenyl)-6-isopropyl-2-(N-methyl-N-methansulfonylamino)-5-pyrimidincarbaldehyd der Strukturformel III



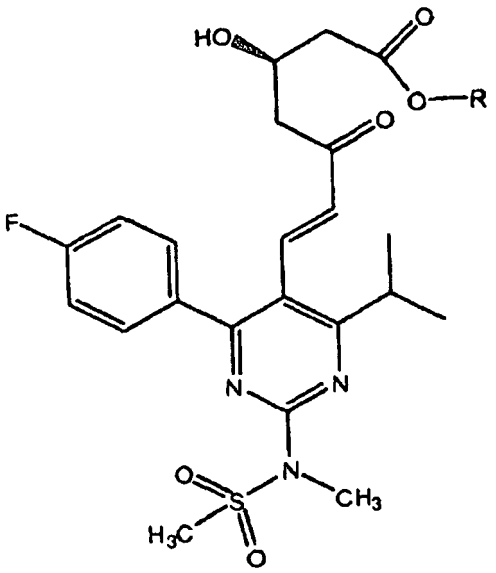
Formel III

zur Bildung eines kondensierten Produkts der Strukturformel IV,



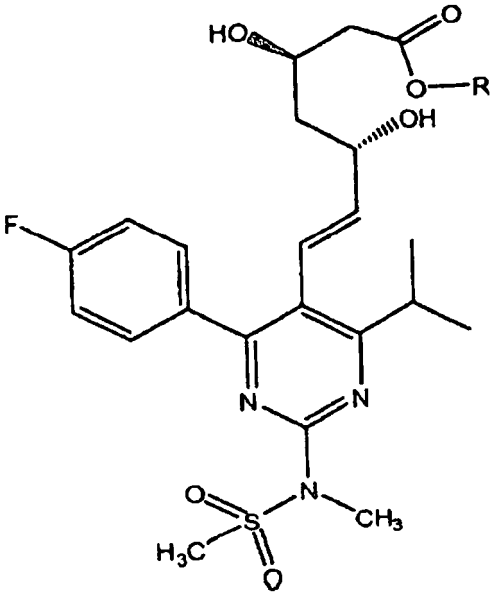
Formel IV

(b) Verestern des kondensierten Produkts zur Bildung eines Esters der Formel IX,



Formel IX

worin R Methyl, Ethyl oder Propyl ist,
(c) Reduzieren des Esters zur Verbindung der Strukturformel X und



Formel X

worin R Methyl, Ethyl oder Propyl ist
(d) Hydrolyse der Verbindung der Strukturformel X zur Herstellung der Verbindung der Strukturformel I in Form der freien Säure, in Form eines Esters oder Laktons von dieser oder in Salzform.

26. Verfahren nach Anspruch 25, wobei der Schritt (a) in einem organischen Lösungsmittel durchgeführt wird.

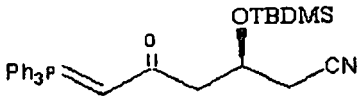
27. Verfahren nach Anspruch 26, wobei das organische Lösungsmittel aus der aus Toluol, Benzol, Cyclohexanen,

Heptanen oder deren Mischung(en) bestehenden Gruppe ausgewählt ist.

28. Verfahren nach Anspruch 27, wobei das organische Lösungsmittel Toluol ist.

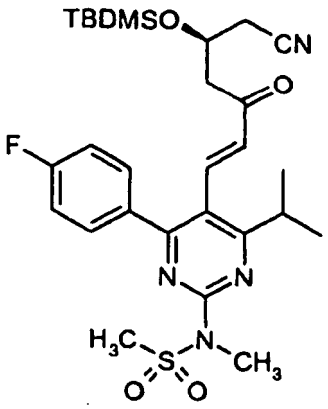
29. Verfahren nach Anspruch 25, wobei der Schritt (b) mit Methanol in Gegenwart von Salzsäure durchgeführt wird.

30. Verbindung der Strukturformel II



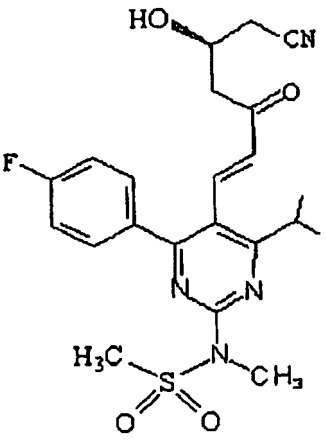
Formel II

31. Verbindung der Strukturformel IV.



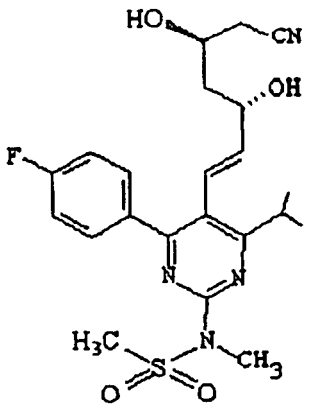
Formel IV

32. Verbindung der Strukturformel V.



Formel V

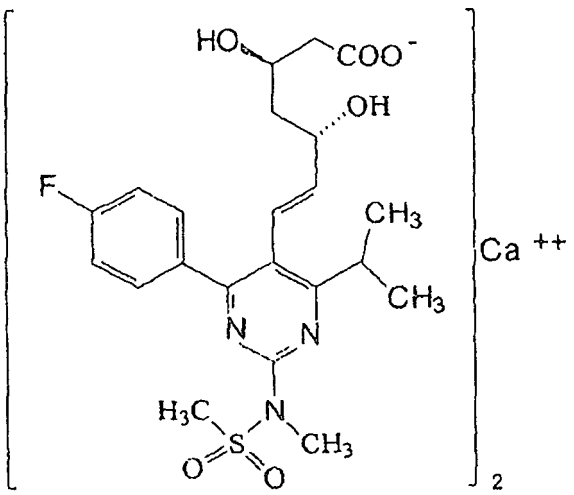
33. Verbindung der Strukturformel VI.



Formel VI

Revendications

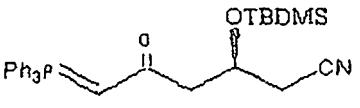
1. Procédé de production de rosuvastatine présentant la formule structurelle I suivante :



FORMULE I

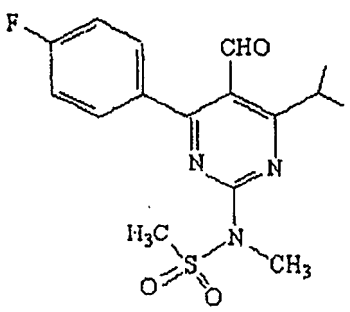
comprenant les étapes consistant à :

a. effectuer la condensation de 1-cyano-(2*S*)-2-[(tert-butyldiméthylsilyl)oxy]-4-oxo-5-triphényl-phosphoranylidène-pentane répondant à la formule structurelle II suivante :



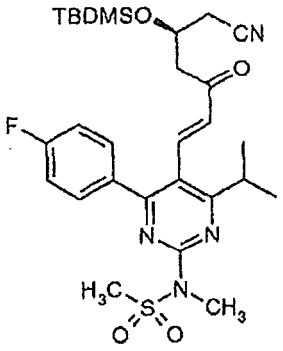
FORMULE II

avec du 4-(4-fluorophényl)-6-isopropyl-2-(N-méthyl-N-méthanesulfonylamino)-5-pyrimidine-carbaldéhyde présentant la formule structurelle III suivante :



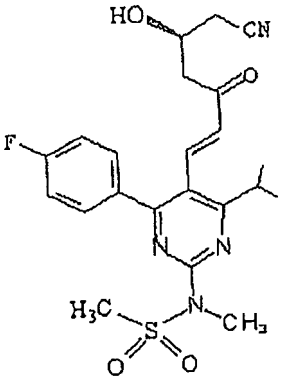
FORMULE III

pour donner un produit condensé répondant à la formule structurelle IV suivante :



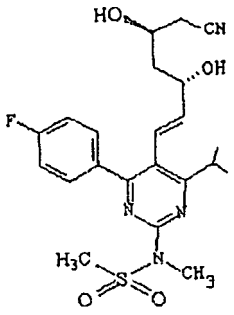
FORMULE IV

b. déprotéger le groupement tert-butyldiméthylsilyle du produit condensé de manière à générer un cyanocétoalcool répondant à la formule structurelle V suivante :



FORMULE V

c. réduire le cyanocétoalcool en cyanodiol répondant à la formule structurelle VI suivante :



FORMULE VI

et

d. hydrolyser le cyanodiol de formule structurelle VI pour produire ledit composé de formule structurelle I sous la forme d'acide libre ou sous la forme d'un ester ou d'une lactone de celui-ci, ou sous la forme d'un sel.

2. Procédé selon la revendication 1, dans lequel l'étape (a) est effectuée dans un solvant organique.

3. Procédé selon la revendication 2, dans lequel le solvant organique est sélectionné dans le groupe constitué du toluène, du benzène, de cyclohexanes, d'heptanes ou de leurs mélanges.

4. Procédé selon la revendication 3, dans lequel le solvant organique est le toluène.

5. Procédé selon la revendication 1, dans lequel l'étape (b) est effectuée dans un solvant organique.

6. Procédé selon la revendication 5, dans lequel le solvant organique est sélectionné dans le groupe constitué du sulfolane, du dioxane, du sulfoxyde de diméthyle, de l'acétamide de diméthyle, de la N-méthylpyrrolidone, de l'acétonitrile, de l'éther de diéthyle, du tétrahydrofurane, du dimethylformamide, du méthanol, de l'éthanol, du propanol et de leurs mélanges.

7. Procédé selon la revendication 6, dans lequel le solvant organique est le méthanol.

8. Procédé selon la revendication 1, dans lequel la déprotection à l'étape (b) est effectuée par traitement avec des acides ou avec du fluorure de tétrabutylammonium.

9. Procédé selon la revendication 8, dans lequel les acides sont des acides sulfoniques, des acides inorganiques ou des acides organiques.

10. Procédé selon la revendication 9, dans lequel les acides sont sélectionnés dans le groupe constitué de l'acide méthanesulfonique, de l'acide trifluorométhanesulfonique, de l'acide chlorhydrique, de l'acide sulfurique, de l'acide nitrique, de l'acide phosphorique, de l'acide formique, de l'acide trifluroacétique et de l'acide acétique.

11. Procédé selon la revendication 10, dans lequel l'acide est l'acide méthanesulfonique.

12. Procédé selon la revendication 1, dans lequel la réduction à l'étape c est effectuée en présence de diéthylméthoxyborane et de borohydrure de sodium.

13. Procédé selon la revendication 12, dans lequel la réduction est effectuée dans un mélange de solvants organiques comprenant des solvants de type alcool et des solvants non alcooliques.

14. Procédé selon la revendication 13, dans lequel l'alcool est sélectionné dans le groupe constitué du méthanol, de l'éthanol, du propanol et du butanol.

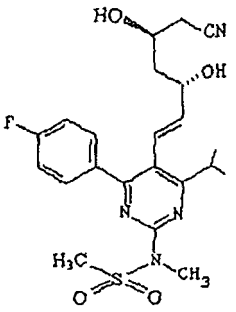
15. Procédé selon la revendication 14, dans lequel l'alcool est le méthanol.

16. Procédé selon la revendication 13, dans lequel le solvant non alcoolique est sélectionné dans le groupe constitué de l'acétonitrile, de l'éther de diéthyle, du tétrahydrofurane et du diméthyl-formamide.

17. Procédé selon la revendication 16, dans lequel le solvant organique non alcoolique est le tétrahydrofurane.

18. Procédé selon la revendication 1, dans lequel l'hydrolyse à l'étape (d) est effectuée après que la réaction à l'étape c est terminée.

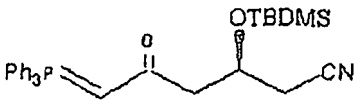
19. Procédé de préparation d'un composé présentant la formule structurelle VI suivante :



FORMULE VI

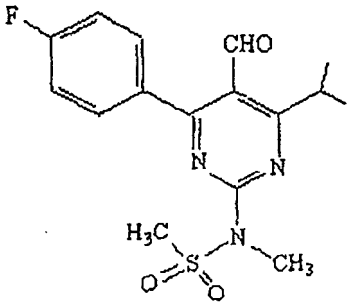
comprenant les étapes consistant à :

a. effectuer la condensation de 1-cyano-(2S)-2-[(tert-butyldiméthylsilyl)oxy]-4-oxo-5-triphényl-phosphoranylidène-pentane répondant à la formule structurelle II suivante :



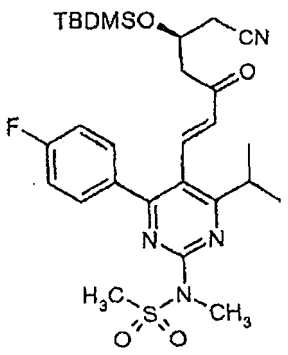
FORMULE II

avec du 4-(4-fluorophényl)-6-isopropyl-2-(N-méthyl-N-méthanesulfonylamino)-5-pyrimidine-carbaldéhyde de formule structurelle III suivante :



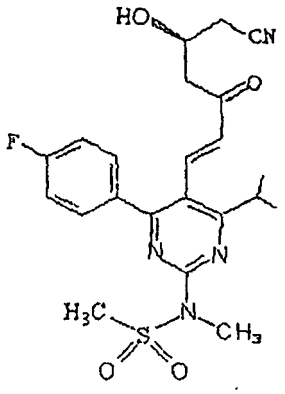
FORMULE III

pour donner un produit condensé répondant à la formule structurelle IV suivante :



FORMULE IV

b. déprotéger le groupement tert-butyldiméthylsilyle du produit condensé pour générer un cyanocétoalcool de formule structurelle V suivante :

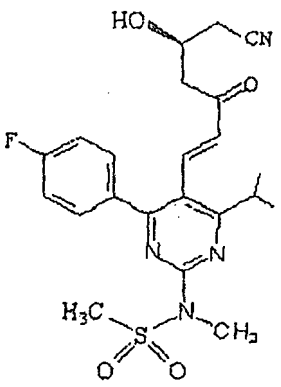


FORMULE V

et

c. réduire le cyanocétoalcool de formule structurelle V pour produire ledit composé répondant à la formule structurelle VI.

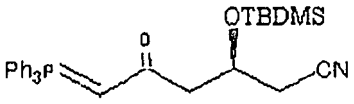
20. Procédé de préparation d'un composé présentant la formule structurelle V suivante :



FORMULE V

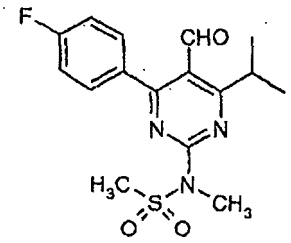
comprenant les étapes consistant à :

(a) effectuer la condensation de 1-cyano-(2S)-2-[(tert-butyldiméthylsilyl)oxy]-4-oxo-5-triphényl-phosphoranylidène-pentane répondant à la formule structurelle II suivante :



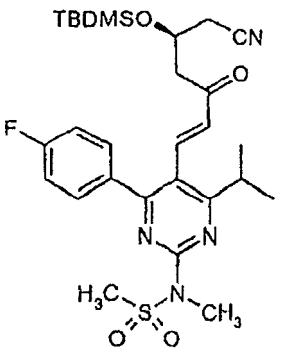
FORMULE II

avec du 4-(4-fluorophényl)-6-isopropyl-2-(N-méthyl-N-méthanesulfonylamino)-5-pyrimidine-carbaldéhyde présentant la formule structurelle III suivante :



FORMULE III

pour donner un produit condensé répondant à la formule structurelle IV suivante :

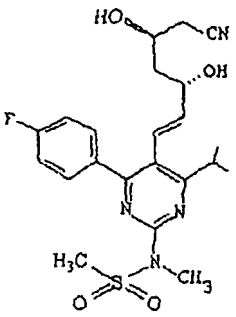


FORMULE IV

et

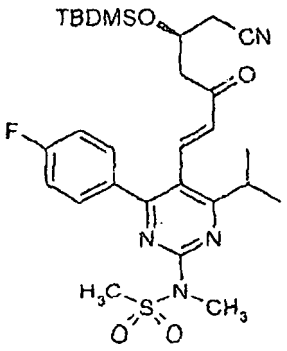
b. déprotéger le groupement tert-butyldiméthylsilyle du produit condensé pour donner ledit composé répondant à la formule structurelle V.

21. Procédé selon la revendication 20, comprenant en outre la réduction du composé présentant la formule structurelle V pour produire un composé répondant à la formule structurelle VI suivante :



FORMULE VI

22. Procédé de préparation d'un composé présentant la formule structurelle IV suivante :

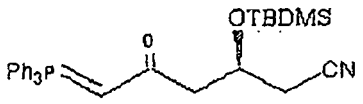


FORMULE IV

comprenant les étapes consistant à :

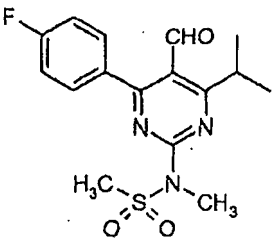
- effectuer la condensation de 1-cyano-(2*S*)-2-[(tert-butyldiméthylsilyl)oxy]-4-oxo-5-triphényl-phosphoranylidè-

ne-pentane répondant à la formule structurelle II suivante :



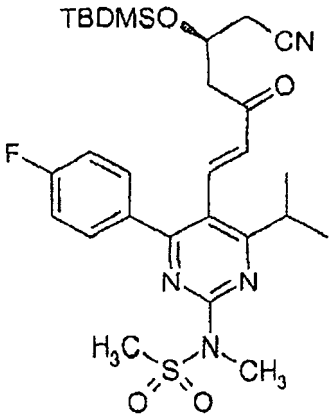
FORMULE II

avec du 4-(4-fluorophényl)-6-isopropyl-2-(N-méthyl-N-méthanesulfonylamino)-5-pyrimidine-carbaldéhyde répondant à la formule structurelle III suivante :



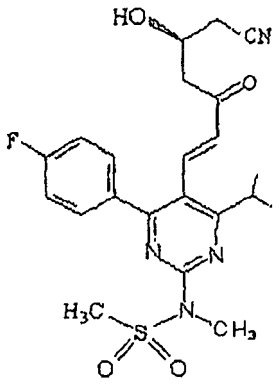
FORMULE III

pour donner un produit condensé répondant à la formule structurelle IV suivante :



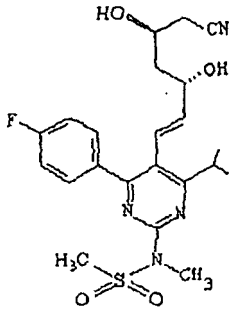
FORMULE IV

23. Procédé selon la revendication 22, comprenant en outre la déprotection du groupement tert-butyldiméthylsilyle du produit condensé pour générer un composé présentant la formule structurelle V suivante :



FORMULE V

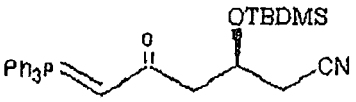
24. Procédé selon la revendication 23, comprenant en outre la réduction du composé présentant la formule structurelle V pour produire un composé répondant à la formule structurelle VI suivante :



FORMULE VI

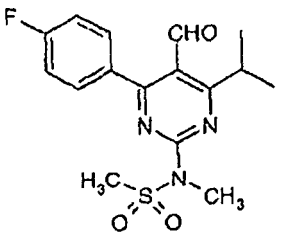
25. Procédé de production de rosuvastatine présentant la formule structurelle I comprenant les étapes consistant à :

(a) effectuer la condensation de 1-cyano-(2S)-2-[(tert-butyldiméthylsilyl)oxy]-4-oxo-5-triphényl-phosphoranylidène-pentane répondant à la formule structurelle II suivante :



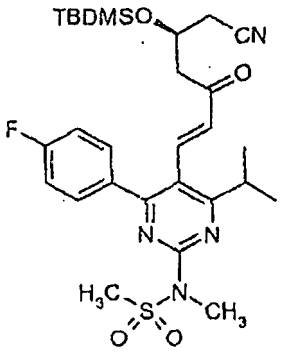
FORMULE II

avec du 4-(4-fluorophényl)-6-isopropyl-2-(N-méthyl-N-méthanesulfonylamino)-5-pyrimidine-carbaldéhyde présentant la formule structurelle III suivante :



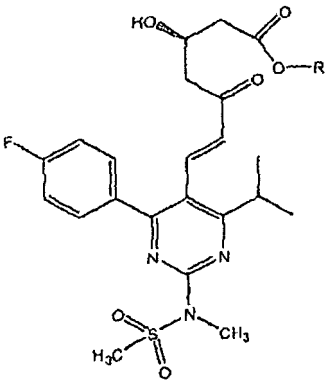
FORMULE III

pour donner un produit condensé répondant à la formule structurelle IV suivante :



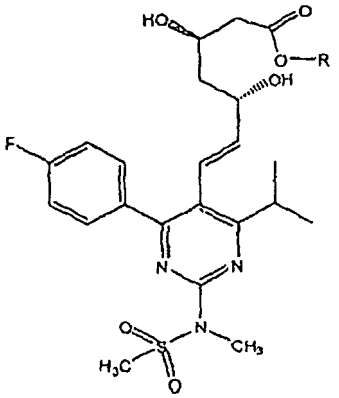
FORMULE IV

(b) estérifier le produit condensé pour générer un ester présentant la formule IX suivante :



FORMULE IX

dans laquelle R représente un méthyle, un éthyle ou un propyle ;
(c) réduire l'ester en composé présentant la formule structurelle X suivante :



FORMULE X

dans laquelle R représente un méthyle, un éthyle ou un propyle ;
et

(d) hydrolyser le composé présentant la formule structurelle X pour produire ledit composé répondant à la formule structurelle I sous la forme d'acide libre ou sous la forme d'un ester ou d'une lactone de celui-ci, ou sous la forme d'un sel.

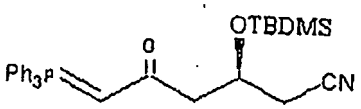
26. Procédé selon la revendication 25, dans lequel l'étape (a) est effectuée dans un solvant organique.

27. Procédé selon la revendication 26, dans lequel le solvant organique est sélectionné dans le groupe constitué du toluène, du benzène, de cyclohexanes, d'heptanes ou de leurs mélanges.

28. Procédé selon la revendication 27, dans lequel le solvant organique est le toluène.

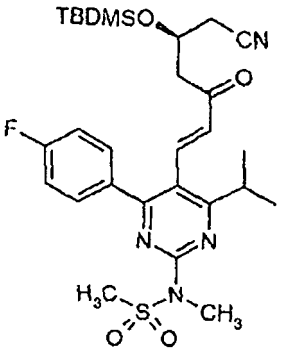
29. Procédé selon la revendication 25, dans lequel l'étape (b) est effectuée avec du méthanol en présence d'acide chlorhydrique.

30. Composé présentant la formule structurelle II suivante :



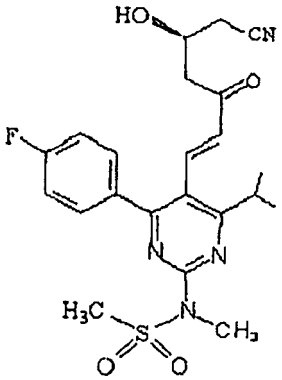
FORMULE II

31. Composé présentant la formule structurelle IV suivante :



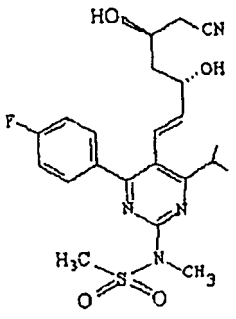
FORMULE IV

32. Composé présentant la formule structurelle V suivante :



FORMULE V

33. Composé présentant la formule structurelle VI suivante :



FORMULE VI

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- US 5260440 A **[0006] [0022]**